THE SYNTHESIS OF SOME GLYOXALINE DERIVATIVES

BY

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

JOHN RAVEN JOHNSON

ENTITLED THE SYNTHESIS OF SOME GLYOXALINE DERIVATIVES.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF BACHELOR OF SCIENCE IN CHEMISTRY

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I wish to express my sincere thanks and appreciation to Professor Roger Adams, for the interest he has shown in this investigation, and for the many valuable suggestions he has offered. I wish also to thank Mr. Carl S. Marvel, who has given much practical assistance in the choice of laboratory methods.

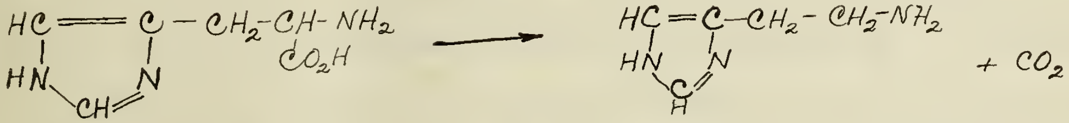
John R. Johnson.

CONTENTS

The Synthesis of Some Glyoxaline Derivatives

Introductory

This investigation was undertaken with the idea of preparing β-imidazolyl ethyl amine, (4 β-aminoethyl glyoxaline) and some of its derivatives, and studying these various derivatives with particular regard to their physiological activity. This amine is formed from the commonly occurring amino acid, histidine, by decarboxylation; a process carried on by the carboxylase bacteria in the large intestine.



Similar amines, (the so-called ptomaines) are obtained by the action of carboxylase bacteria on the other amino-acids and are called by Kutscher1) aporrhegmas; for example,

Amino-Acid	Aporrhegma
Alanine	Ethyl Amine
Phenyl-alanine	Phenyl-ethylamine
Tyrosine	(Hydroxyphenyl)ethylamine, Tyramine
Tryptophane	Indol-ethylamine
Histidine	Imidazolyl-ethylamine, Histamine
Arginine	Tetramethylene diamine, Putrescine and Guanidine-butylamine, Agmatine
Lysine	Pentamethylene diamine, Cadaverine
Leucine	Isoamylamine etc., etc.

Many of these substances have marked physiological activity, and in many cases an effect on the blood pressure. Imidazolylethyl amine decreases the coagulability of the blood, and produces vasodilation, as well as a direct stimulating effect on plain muscle, producing tonic contraction. The muscular coats of the bronchioles are also highly sensitive to the action of this amine, especially in the rodents.

The isolation of this amine offers considerable difficulty in the laboratory and even the production from histidine is not as simple as might be expected. The most convenient method is the synthesis from diaminoacetone hydrochloride, as carried out by Pyman[2]), and this is a long and involved process. (see page 8).

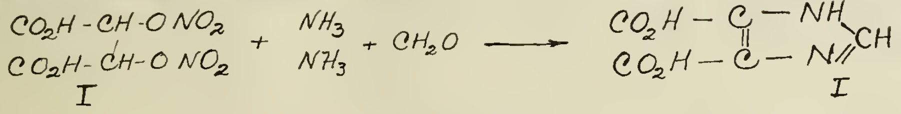
Recently, however, Pyman synthesized 4,5 glyoxaline dicarboxylic acid, in fair yields from tartaric acid, thru the dinitrate[3]). He found that by refluxing this acid with aniline, one carboxyl was split off and the other was converted to the anilid, giving as the product, glyoxaline 4 carboxanilid; or on heating the acid to its melting point, 288°, it loses two molecules of CO_2 and forms glyoxaline, which distills off and may thus be obtained in a pure condition in excellent yields.

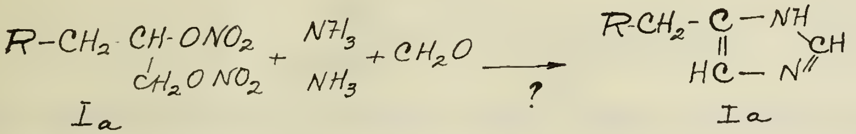
By this means then, glyoxaline, glyoxaline 4 carboxanilid, and 4,5 dicarboxylic acid are made readily available for the synthesis of glyoxaline derivatives; and the following scheme was worked out. This carboxanilid on treatment with phosphorus pentachloride would yield the imidchloride, which on treatment with aqueous sodium cyanide would give glyoxaline 4 carboxanilid imid cyanide. This compound then on reduction with the proper reagent might yield 4 aminoethyl glyoxaline, or certainly a derivative of this substance, which would be likely to have similar physiological properties.

Besides the method of attack indicated above, it was thought possible that diaminoacetone hydrochloride, which is used by Pyman in this synthesis might be obtained by a simpler method. This author starts with citric acid, going thru acetone dicarboxylic acid, and diisonitrosoacetone which on reduction yields the desired diaminoacetone hydrochloride. It was thought that 1,3 dichlorhydrin, (easily made from glycerol and sulfur chloride) might be used as a convenient starting point for this synthesis; for example, by oxidation with chromic acid

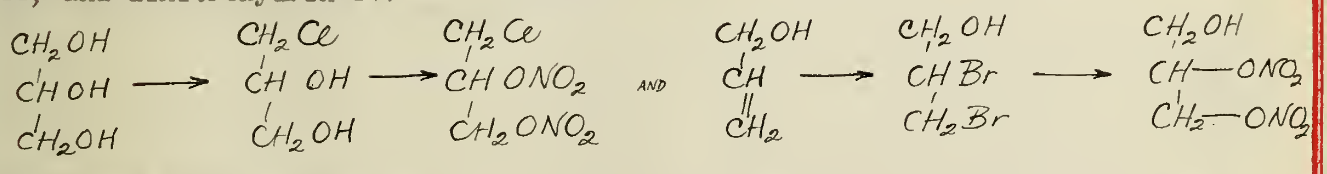
it yields dichloroacetone, and this with potassium phthalimid would yield the diphthalimid derivative of diaminoacetone. On hydrolysis by acid the phthalimid derivative would yield diaminoacetone. Posner[4]) found, however, that the phthalimid derivative of this compound was very insoluble and could not be hydrolyzed by any of the ordinary methods. This author oxidized the diphthalimid derivative of dichlorhydrin with chromic acid[5]) and obtained the ketone derivative. There was some doubt at first as to the structure of this compound, which Posner later explained. Cloez[6]) pointed out that dichloracetone from dichlorhydrin was really an oxide. For these reasons, another method must be used and as a result several methods were tried out.

Another possible method of attack was the preparation of glyoxaline derivatives by the condensation of dinitro esters with ammonia and formaldehyde, in a manner analagous to the preparation of glyoxaline 4,5 dicarboxylic acid, Ia, from the dinitrate of tartaric acid, I; thus,-





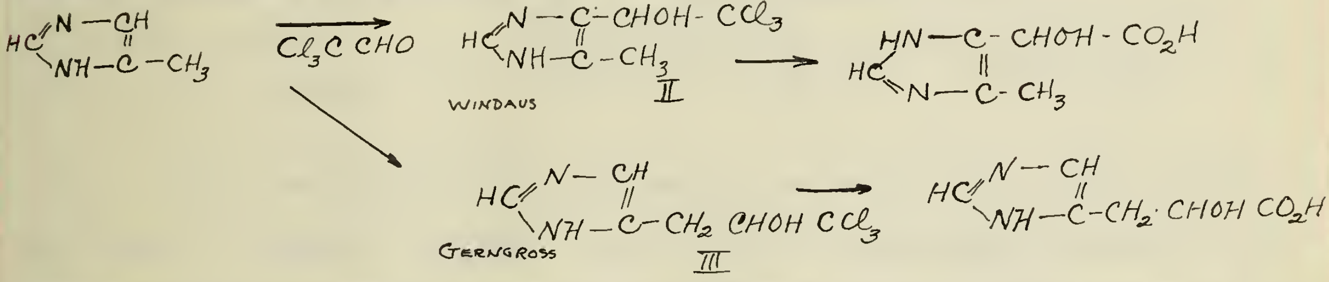
The materials for this synthesis would be readily available from glycerol derivatives; two of the simpler compounds of type II would be chlordinitrohydrin III, and dinitrohydrin IV.



The former would be obtained by the nitration of monochlorhydrin, in the usual manner; the latter by addition of bromine to allyl alcohol, and treatment of the resulting 1,2 dibromhydrin with alcoholic silver or lead nitrate. This general method was not considered very promising, since in the two compounds, III and IV, the nitrate groups are more stable and are not activated as in dinitrotartaric

acid. However, the method was worth trying out, since even a poor yield would make glyoxalines with substituted side chains available for the synthesis of 4 aminoethyl glyoxaline.

The work of Windaus and Knoop7) has also made another glyoxaline derivative available; these authors found that by the action of ammonia[1] on glucose, a nitrogenous base was produced, which they identified as 4 methyl glyoxaline. This substance has already been used by Gerngross in an attempt to synthesise histidine8). This author condensed chloral with methyl glyoxaline, in a manner analagous to the condensation of chloral with quinaldine, and he obtained a substance which he hoped on hydrolysis would yield glyoxaline 4, β-hydroxypropionic acid. He obtained by this means a condensation product of the correct empirical formula, but there is some doubt that this was the desired product. It was shown later by Windaus9) that the product formed was more likely of formula II than III.



Apparently this condensation does not yield simple glyoxaline derivatives as might be expected, but instead 5 methyl, 4 substituted glyoxalines, and these have been shown by Ewins10) to have only one-two hundredth of the activity of those without the methyl group in the 5 position11).

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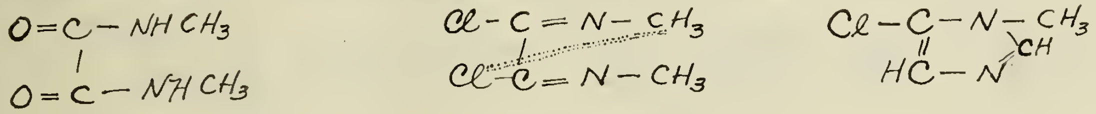
[1] These authors actually used the more highly dissociated zinc complex ammonium hydroxide.

II. Historical

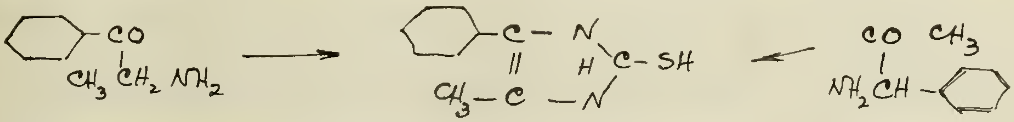
(a) Glyoxaline

Glyoxaline has been known since 1856, when it was discovered by Debus[12] as a product of the reaction between glyoxal and ammonia, and was named from this method of preparation. Radzieszewski[13] in 1882 explained this reaction and showed that it was a general reaction for 1,2 diketones, 1,2 ketonaldehydes, and compounds containing the group R-CO-CO-R, where R may be aryl or alkyl groups, or even hydrogen.

In 1876 Wallach discovered a type of basic compounds which he called oxalines, the most simple of which was formed by the action of phosphorus pentachloride on dimethyl oxamide. The tetrachlor compound loses three moles of hydrochloric acid and gives chloro-N methyl glyoxaline, which on reduction yields N methyl glyoxaline. The reaction has been explained as follows:

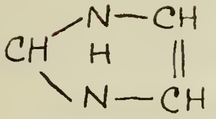


The structural formula of glyoxaline was worked out by Japp in 1882 and his formula is generally accepted. The position of the labile hydrogen is not yet known exactly, however, and there is some question as to the relation of the double bonds. The reason for this is: 4,5 methyl phenyl glyoxaline is formed by oxidation of methyl phenyl glyoxaline mercaptan with nitric acid, by method two (see page 10) and the same methyl phenyl glyoxaline results when 1 amino propiophenone, or the isomeric 1 amino, 1 phenyl acetone is used in Gabriel's method:

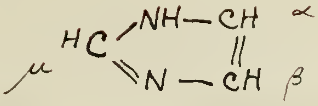


This synthesis shows the equivalence of the nitrogen atoms and also the equivalence of the 4 and 5 positions in unsubstituted glyoxalines. Since the position of the imino hydrogen is thus not accurately known, several reference

works such as Beilstein[14]) write the formula as in formula 1 below. The designation of the positions is shown in II:



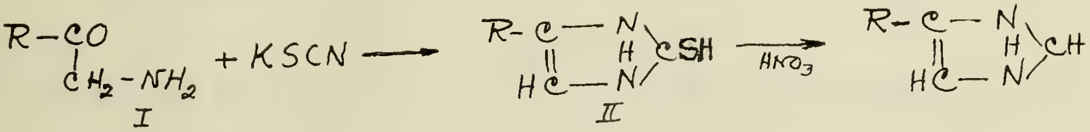
I



II

Altho the formation of glyoxalines from compounds of the type R-CO-CO-R is of most importance historically, its application is limited by the fact that the necessary 1,2 diketones or 1,2 ketonaldehydes are not easily prepared in the laboratory, due in many cases to their great reactivity and tendency to polymerize.

Gabriel and Pinkus[15]) in 1893 discovered that 1,2 aminoketones of the general formula $R-CO-CH_2NH_2$ react with potassium thiocyanate in aqueous solution to form thiolglyoxalines of the general formula, I, and these on oxidation with dilute nitric acid yield glyoxalines of type II.



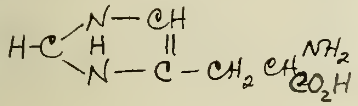
This method has been widely applied in the synthesis of glyoxaline derivatives substituted in the 4,5 positions, since many of these are scarcely possible by the first method. The simple substituted glyoxalines such as 4, methyl, ethyl, propyl, isobutyl, amyl, and etc. have been prepared by this method as well as many of the 4,5 disubstituted derivatives. The most important synthesis carried on along these lines was that of Pyman in 1911[2]). This author condensed diamino-acetone, hydrochloride with potassium thiocyanate and obtained 4 amino-methyl 2 thiolglyoxaline, from which he synthesised 4 aminoethyl glyoxaline, (β-imidazolyl ethyl amine), and several related compounds (see page 8).

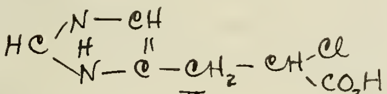
(b) 4 β-amino ethyl glyoxaline
β-Imidazolyl Ethyl Amine

This amine was first prepared by Windaus and Vogt[16]) in 1907 by the

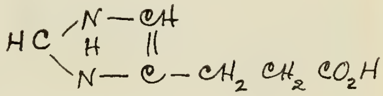
application of Curtius's method to imidazolyl propionic acid. This acid may be obtained by synthesis or by the reductive deaminization of histidine. The amine is obtained from histidine, by bacterial action, and in this manner small amounts may be formed in the large intestine and then enter the blood stream.32)

Windaus and Vogt prepared the amine by an indirect decarboxylation of histidine; the latter is converted into 4 glyoxaline chloropropionic acid, II, (by treatment with sodium nitrite and hydrochloric acid); this is reduced to 4 glyoxaline propionic acid, III, which is esterified, IV, and then converted to the hydrazide, V. The latter is then converted to the azide and urethane (by amyl nitrite and hydrogen chloride, in alcoholic solution) and the latter on hydrolysis with acid gives the salt of the amine.

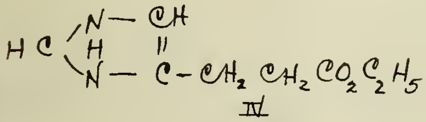




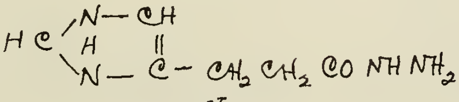
II



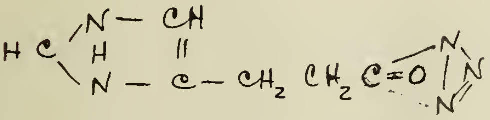
III

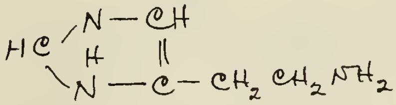


IV



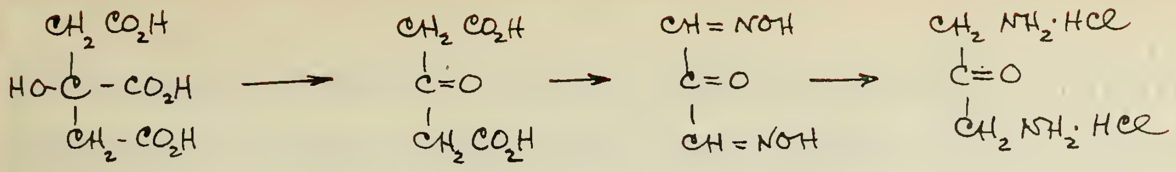
V.



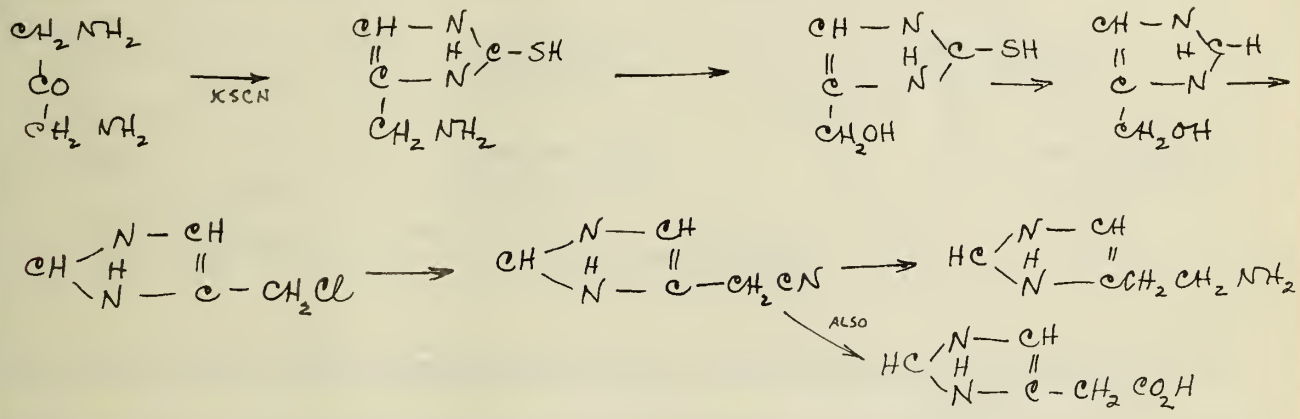


Pyman's synthesis of this amine has already been mentioned, and is the most convenient. It depends on the discovery of Gabriel and Pinkus, that aminoacetonehydrochloride on heating with aqueous potassium thiocyanate, yields 4 methyl 2 thioglyoxaline, and the latter on oxidation yields 4 methyl glyoxaline.

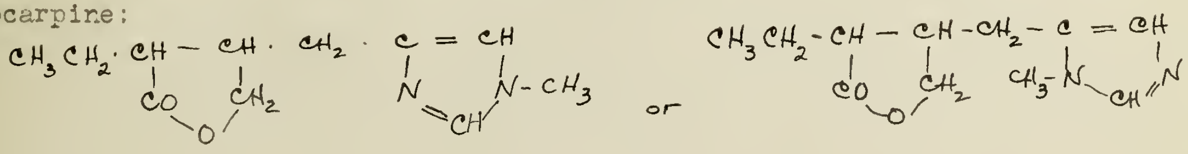
In his synthesis, Pyman used diaminoacetone hydrochloride which he obtained from citric acid by the following method: Citric acid was treated with fuming sulphuric acid according to the directions of Pechmann17) and yields acetone dicarboxylic acid, II, and this by the action of sodium nitrite and acid gives diisonitrosoacetone. The latter on reduction with stannous chloride by the method of Kalischer18) is converted into diaminoacetone hydrochloride.



Diaminoacetone hydrochloride on heating with aqueous potassium thiocyanate forms 2 thiol 4 amino-methyl glyoxaline, and this on oxidation with HNO_3 yields 4 hydroxymethyl glyoxaline, since the free nitrous acid formed in the reaction acts on the amino group and hydrolyzes to the alcohol. The alcohol on treatment with phosphorus pentachloride gives 4 chloromethyl glyoxaline, and the latter with aqueous potassium cyanide gives 4 cyanomethyl glyoxaline. The cyano derivative on reduction with sodium and alcohol yields the desired amine, 4 aminoethyl glyoxaline, along with large amounts of 4 glyoxaline acetic acid.



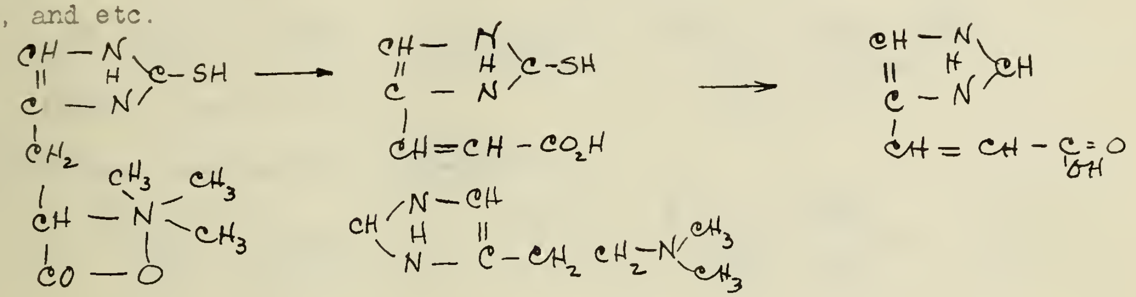
Among the more important derivatives of glyoxaline which occur in nature are the alkaloids of Jaborandi, pilocarpine and isopilocarpine, and their related compounds and decomposition products. The alkaloid pilocarpine, was discovered by Hardy in 1875 and the constitution was investigated by Hardy and Calmels shortly after, but the formula which they advanced was shown later to be incorrect. The present knowledge of this group of alkaloids has largely been worked out by Jowett[19]) and by Pinner and Schwarz[20]), who have given the following formula for pilocarpine:



This formula was confirmed by Pyman[21]) in 1910, the only point of doubt being the position of the methyl group with respect to the 4 and 5 positions. This author also succeeded in preparing several compounds allied to pilocarpine, and studied their physiological activity; he did not succeed in obtaining any which showed a similar action.

Isopilocarpine on distillation with soda-lime[22]) yields simple glyoxaline derivatives such as 1 methyl glyoxaline, 1, 4(or 1,5) dimethyl glyoxaline, and 1,4 (or 1,5) methyl amyl glyoxaline.

Glyoxaline complexes also occur in the extracts of Claviceps purpurea, (ergot); e.g., Ergothionene and its decomposition products, 4 aminoethyl glyoxaline, and etc.



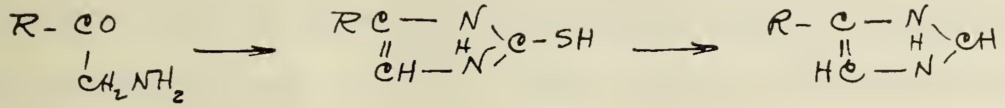
For a long time, p-hydroxyphenylethyl amine was thought to be the active constituent of ergot extracts, but Barger and Dale[23]) and others have shown that 4 aminoethyl glyoxaline is of more importance, and is more closely associated with the physiological activity of ergot.

III. Theoretical.

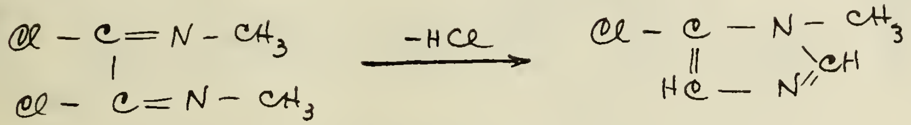
The general methods of preparation of glyoxaline derivatives are:

1. From compounds of the type R-CO-CO-R by treatment with ammonia and an aldehyde:12)

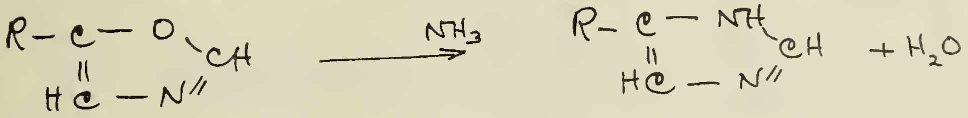
2. From compounds of the type R-CO-CH$_2$NH$_2$ by treatment with potassium thio cyanate, and oxidation of the resulting thiolglyoxaline with nitric acid:15)



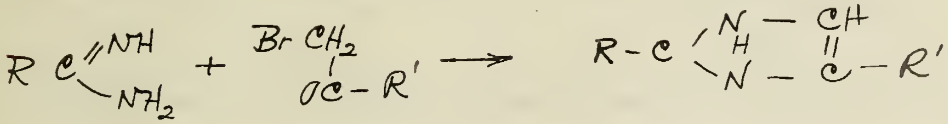
3. From alkyl imidchlorides chlorsubstituted glyoxalines are formed:24)



4. By heating oxazoles with ammonia:25)



5. By the condensation of amidines with 1,2 halogen ketones:26)



The methods above are the most important means of synthesis of glyoxaline derivatives, and thus there were five methods of approaching the problem. Since it would not be possible to investigate all of the possible methods, those used were limited to the first two methods.

The methods used in this investigation will be divided into three groups according to the substance used as a starting point for the synthesis:

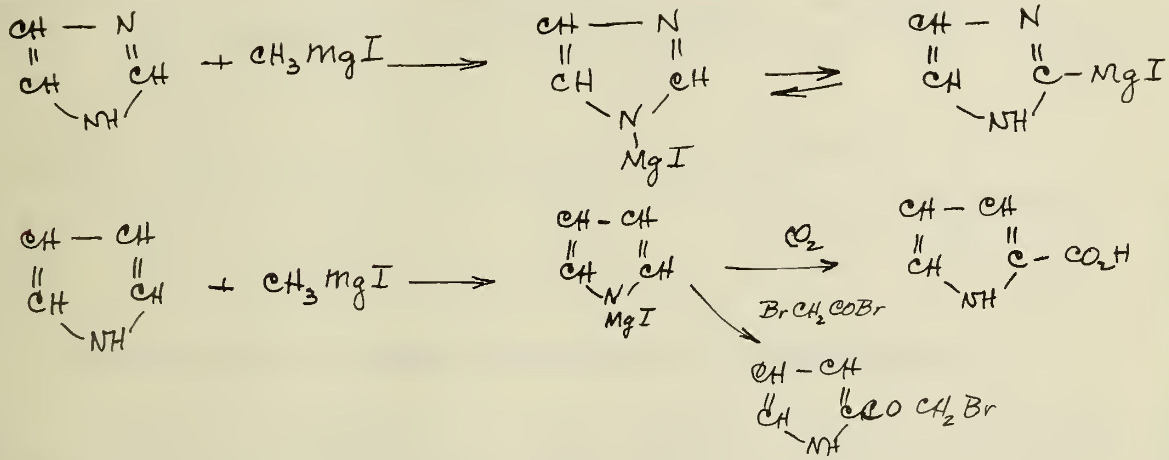
(1) Compounds of the type R-CO-CO-R.

(2) Compounds of the type R-CO-CH$_2$NH$_2$ (etc)

(3) Other Methods.

COMPOUNDS OF THE TYPE R-CO-CO-R

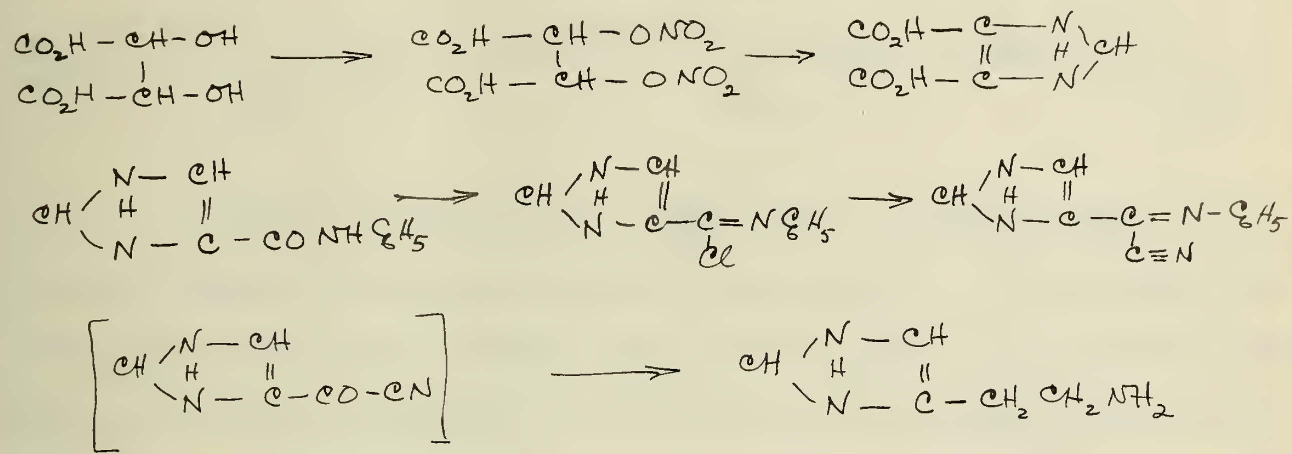
(a) The simplest substance of this group is glyoxal itself, which yields glyoxaline on treatment with ammonia and formaldehyde. Glyoxaline may be prepared by this method but the yields are poor. This substance might be made the starting point if it would react with alkyl magnesium halides to give glyoxaline magnesium halides. This reaction would be analagous to the preparation of the magnesium pyrrol halides by the treatment of pyrrol with alkyl magnesium halides. In the latter case the reaction proceeds readily and is very useful for the preparation of derivatives; e.g., with carbon dioxide the monocarboxylic acid is formed, and etc.



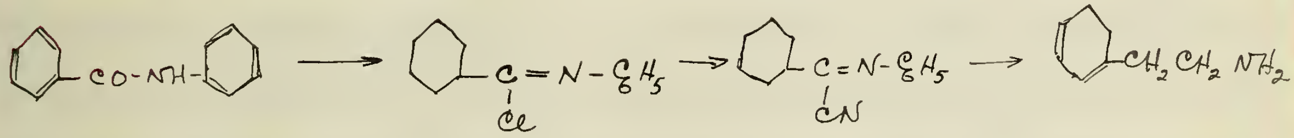
In the case of glyoxaline if the magnesium derivative could be formed, it would yield glyoxaline chlormethyl ketone on treatment with chloracetyl chloride, and the latter on conversion to the amine and subsequent reduction would give the desired amine.

(b) Glyoxaline 4,5 dicarboxylic acid is formed by the treatment of dinitro tartaric acid with ammonia and formaldehyde, and on boiling with aniline forms the monocarboxanilid. If the latter compound acted as an ordinary anilid, on treatment with phosphorus pentachloride it would yield the glyoxaline 4 carboxanilid imide chloride. The imide chloride on treatment with aqueous sodium cyanide would yield the imide cyanide, and this on reduction would yield glyoxa-

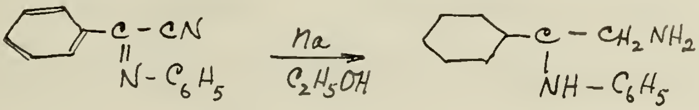
line ethyl amine or a derivative. Since the glyoxaline derivative was somewhat difficult of preparation it was decided to try out the reaction starting with benzanilid. This was satisfactory because the glyoxaline derivatives act very much the same as benzol derivatives toward the ordinary reagents, and are if anything more stable. Another advantage is the fact that the benzol derivatives formed, would be more easily identified since they have in most cases been prepared. Starting with tartaric acid the reactions are as follows:



Starting with the benzol derivatives the reactions are:

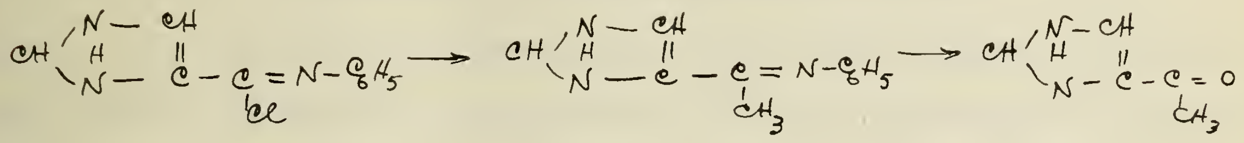


The synthesis was started using benzanilid, and the imid chloride and cyanide were easily prepared. The latter was reduced with sodium and alcohol in the ordinary manner for the reduction of nitriles and the resulting amine was not however the desired phenylethylamine, but a diamine, showing that the anilid group was not hydrolyzed off as desired, but was reduced. Apparently the reaction took place as follows:

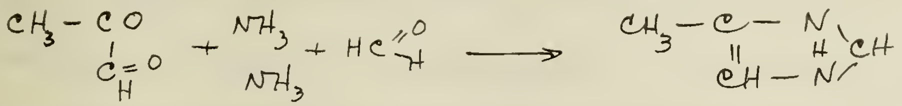


Even though this synthesis did not give the desired compound it was decided to prepare the imidazol derivative and the hydroxyphenyl derivative and see what physiological activity these would have in comparison to phenyl ethyl amine. This was taken up as a side issue of the main problem.

The imid chloride might also be used in a Grignard reaction with excess of methyl magnesium iodide30) and would then yield glyoxaline methyl ketone, from which the amine could be synthesised. The reaction is:



(c) Methyl 4 glyoxaline might also be used as a starting point, since it is easily formed from glucose and ammoniacal zinc hydroxide. This compound should behave very much the same as toluene toward oxidizing agents, and therefore might either be oxidized, or brominated. In the first case the alcohol might be produced, from which glyoxaline has already been synthesised; or if the oxidation proceeded as far as the aldehyde, this could be condensed with nitromethane and the resulting compound reduced, as in the preparation of ethyl amine derivatives from aromatic aldehydes27). Since the production of methyl glyoxaline involves six weeks standing, it was thought best to start the reaction during the summer and finish it in the fall, since the methyl glyoxaline would not be ready before that time. This formation of methyl glyoxaline is explained as follows, on the presumption that methyl glyoxal is formed from the glucose.



(d) Closely associated with this method, is the preparation of derivatives of isonitrosoacetone. This compound is formed by treatment of acetone with amyl nitrite and hydrogen chloride and gives methyl glyoxal on hydrolysis. If the isonitrosoacetone were halogenated in such a manner that the halogen entered on

the methyl group, and the halogen subsequently replaced by an acetate group, the compound on hydrolysis would give hydroxymethyl glyoxal, and this on treatment with ammonia and formaldehyde would give hydroxymethyl glyoxaline, from which Pyman has synthesised the desired amine. It might be possible to use the isonitrosohalogenated acetone directly in the synthesis by treating it according to method two, that is, condensing it with thiourea.

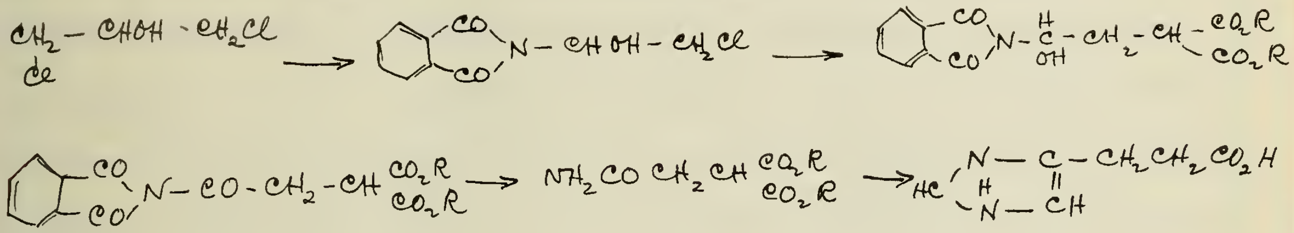
COMPOUNDS OF THE TYPE R-CO-CH_2-NH_2 and etc.

The synthesis from diaminoacetone falls into this group, and therefore the attempted improvement of the preparation of this compound might be mentioned here. It was thought at first that dichloroacetone, from the oxidation of 1,3 dichlorhydrin might be conveniently used, but it seems that this compound is not really s-dichloroacetone but an isomer. The difficulty is also encountered that the diphthalimid derivative of dichloracetone, which would be the natural method of preparing the diamine, is very difficult to hydrolyze. This might be overcome however by using succinimide which gives more soluble products.

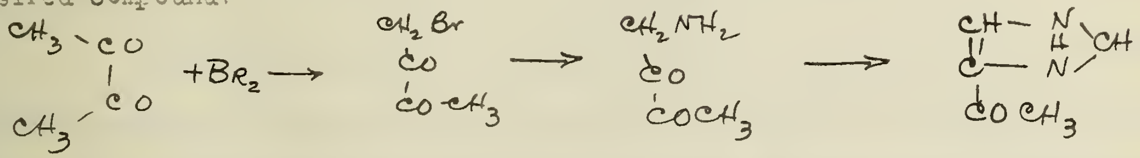
The method of Delepin of preparing amines by the addition of hexamethylene tetramine to halogen compounds was also tried on 1,3 dichlorhydrin to see if it could be applied in this case, and if successful in this trial would be used on dichloracetone. Since the production of dichloracetone from dichlorhydrin is not successful it was necessary to find another method. The only available method seemed to be the direct chlorination of acetone. This was done by Fritsch[28]) and a yield of symmetrical dichloracetone of less than 10 percent was obtained by him. This method did not seem so promising as at first. Another possibility along this line was the preparation of s-diiodo acetone by the action of iodine trichloride on acetone. This is a poor reaction however, since for every mole of the diiodo compound obtained, three moles of monochloracetone are produced.

$$4CH_3COCH_3 + 2ICl_3 \longrightarrow 3CH_3COCH_2Cl + \underset{I}{CH_2}-CO-\underset{I}{CH_2} + 3HCl$$

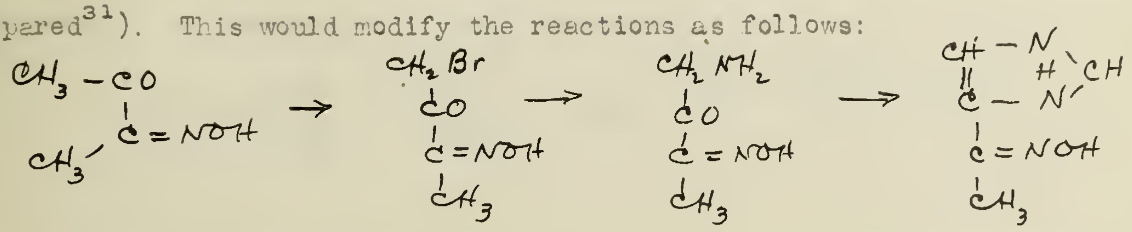
(a) One of the most promising methods along this line would be the condensation of dichloracetone with one mole of phthalimide or succinimide, treating the monohalogen compound resulting, with sodium malonic ester and forming a compound of the type $H_2N-CO-CH_2-CH(CO_2R)_2$. This compound would then yield a glyoxaline derivative by method two, and on hydrolysis and loss of carbon dioxide would give imidazol propionic acid. Imidazol ethyl amine has already been synthesised from this compound (see page 7). Since dichlorhydrin is more easily prepared than dichloracetone, it was thought that it might be worth while to form the compound $C_6H_4(CO)_2N.CHOH.CH_2.CH(COOR)_2$ and see if it could be readily oxidized to the ketone, which is necessary for the reaction. This reaction would also serve to try out the general reaction, and give some idea as to the yields.



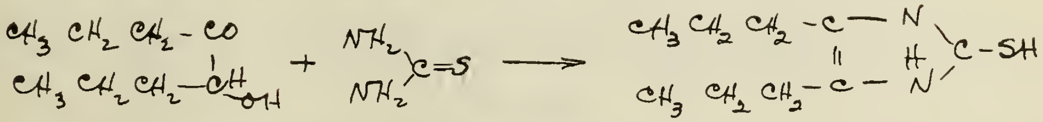
(b) Along this same line would be the bromination of diacetyl to form monobrom diacetyl, conversion to the amine, treatment with potassium thiocyanate and oxidation of the thioglyoxaline to form methyl glyoxaline ketone. The latter on bromination, conversion to the amine, and subsequent reduction would give the desired compound.



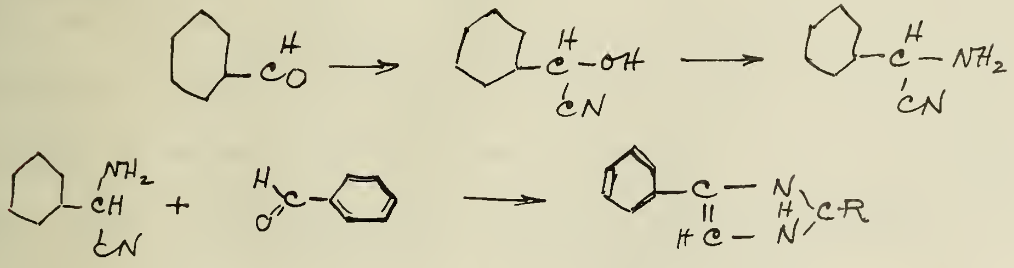
Instead of diacetyl itself, the monoxim might be used in this reaction, since the latter is much more easily prepared and the mono brom derivative has also been prepared[31]). This would modify the reactions as follows:



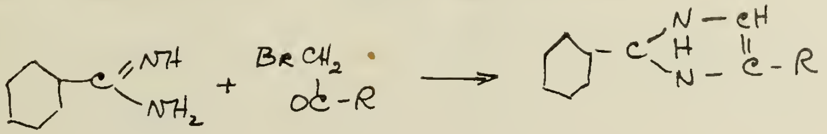
(c) Although aminoketones have been used most widely for the condensation by method two, it was found that hydroxy ketones condensed with thiourea or ammonium thiocyanate[29]) to form thiolglyoxalines in much the same manner. Thus butyroin yields dipropyl thiolglyoxaline:



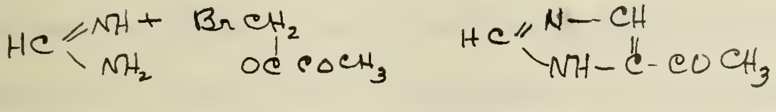
Since the hydroxy and amino compounds condense so readily with thiocyanates or thio urea in the former case, and these are usually formed from the halogen compounds, it would be very convenient if 1,2 halogen ketones would condense with thiourea in a similar manner. Accordingly the condensation of chloracetophenone with thiourea was attempted. This compound was used first because the product formed could be easily identified and purified, and because the material was readily available. If this condensation be successful then other halogen ketones would be tried, in the aliphatic series to see if the reaction were in any way limited to aromatic compounds as is the synthesis of glyoxalines from amino nitriles[25])



One of the methods of synthesis of glyoxalines which was at first rejected because of the inability to prepare the compounds to start with, was later reconsidered when it was found that the starting point was not as difficult as expected. This method is the synthesis discovered by Kunckell[26]); namely, the condensation of amidines with alpha halogen ketones:



This author worked only with compounds in the aromatic series but there is no reason to believe that the reaction could not be applied in the aliphatic series. If formamidin (prepared from hydrocyanic acid and hydrochloric acid and alcohol) is condensed with monobromdiacetyl, the resulting compound would be glyoxaline methyl ketone, which could be converted to the desired amine.



Other Methods

The other method which seemed most promising was the condensation of 1,2 dinitrates with ammonia and formaldehyde in a manner similar to the preparation of glyoxaline 4,5 dicarboxylic acid from the dinitrate of tartaric acid. For the starting point in this method monochlorhydrin, (glycerol monochloride, from glycerol and hydrochloric acid) was used. This was nitrated by treatment with a mixture of fuming nitric and concentrated sulphuric acids and the dinitrochlorhydrin was treated with formaldehyde and ammonia. It was found that after standing for over a week no apparent reaction has taken place. This method was therefore considered useless. The reason that this dinitrate did not react in a manner similar to tartaric acid dinitrate was because it does not possess the two carboxyl groups which tend to make the latter much more unstable. In fact the latter compound in aqueous solution is not stable above 0°.

Experimental.

1. Preparation of Glyoxaline 4,5 Dicarboxylic Acid.[3])

(a) Dinitrotartaric Acid.

25 grams of pulverized tartaric acid are dissolved in 100 cc. of fuming nitric acid, (spec.grav. 1.52) and 100 cc. of sulphuric acid (spec.grav. 1.84) are added with stirring. The mixture warms up and soon crystals are deposited. After stirring for a short while with a glass rod, the mixture solidifies to a thick paste. The nitrotartaric acid is filtered off in a funnel provided with a platinum cone and pad of glass wool, and is sucked as free as possible from the acids. Pyman washes with 50 percent H_2SO_4, but it was found that this agent dissolves considerable quantities of the material, and it was therefore decided to use a stronger acid or not wash at all.

(b) Glyoxaline 4,5 dicarboxylic acid.

The crude nitrotartaric acid is mixed with 150 grams of ice and stirred until all is dissolved. The solution is then placed in a freezing mixture of salt and ice and cooled to about -10° in a vessel provided with an efficient mechanical stirrer. 150 cc. of aqueous ammonia (spec.grav. 0.90) are then added slowly thru a dropping funnel and the temperature is kept as far as possible below 0°. After the ammonia has all been added, 75 cc. of aqueous 40 percent formaldehyde are added, observing the same precautions as to temperature. The mixture is allowed to stand in the freezing bath over night, is then removed and allowed to come slowly to room temperature. About 100-125 cc. of alcohol are then added, and the mixture is acidified with hydrochloric acid. The glyoxaline 4,5 dicarboxylic acid is precipitated and is filtered off, washed with water and finally 95 percent alcohol. The yield varies from 4 to 10-12 grams depending on the temperature control. Glyoxaline 4,5 dicarboxylic acid forms colorless crystals melting with decomposition at 288°. It is insoluble in water, alcohol,

and other organic solvents. On heating to its melting point it is converted into glyoxaline, with loss of CO_2.

In this preparation there are several difficulties which arise. It is very difficult to remove the acids from the nitrotartaric acid, and on the subsequent addition of ammonia, much heat is evolved, which necessitates the very slow addition of the latter. In the preparation of nitrotartaric acid according to Vanino[36]), the crude acid is added in small portions to a mixture of ether and ice. This method was tried and it was found that the ether was oxidized very violently by the nitric acid and large quantities of acetaldehyde are formed as apparent by a strong odor of the same. This would not be a possible method of removing the acids then, since the acetaldehyde would react with the ammonia and nitrotartaric acid and produce 2methyl glyoxaline 4,5 dicarboxylic acid. One other method suggested itself however, and will be tried out later. This is, to dissolve the nitrotartaric acid in small portions in methyl alcohol, and the formaldehyde and formic acid thus formed will not interfere with the reaction. It is stated that the ethyl alcoholic solution of the nitrotartaric acid is more stable than the aqueous and it might also be expected that the methyl alcoholic solution would be more stable. It might also be well to carry out the entire reaction in methyl alcohol solution using solutions of ammonia and of formaldehyde in this solvent.

It is also very necessary to keep the temperature of the reaction mixture below 0° during the addition of the ammonia as well as the formaldehyde. In several trials where the ammonia or formaldehyde was run in too rapidly, the yields were very much lowered.

(c) Glyoxaline.

5 grams of crude glyoxaline dicarboxylic acid are placed in a small distilling bulb, the side tube of which is provided with an air condenser and

heated slowly with a free flame. The material melts at about 280° and at this temperature much gas is evolved and glyoxaline is formed. The dicarboxylic acid used was not previously dried and therefore the glyoxaline contained water and did not solidify. The distillate was washed with about 5 cc. of ether which took up the moisture and caused the glyoxaline to separate as a white crystalline solid of ammoniacal or fishy odor. This ether treatment was repeated with another run of 5 grams of the dicarboxylic acid and could not be duplicated. This may have been because a different sample of acid was used, which contained more moisture. It is therefore essential to the success of the preparation of glyoxaline by this method to use perfectly dry material.

2. Preparation of Glyoxaline 4 Carboxanilid.[3])

15 grams of the glyoxaline 4,5 dicarboxylic acid are refluxed with 150 cc. of aniline, for ten hours and the excess of aniline then removed by steam distillation. The mixture was then cooled and the anilid filtered off. The product is washed with dilute HCl and water, and then a small quantity of alcohol and finally ether. The yield was 6 grams. The product is fairly soluble in alcohol, so too much must not be used for washing. From this point on, benzol derivatives were used to try out the reactions.

3. Preparation of Benzanilid Imid Chloride.[33])

110 grams of PCl_5 (1 mole) are placed in a 500 cc. flask provided with a reflux condenser, and to this are added 150 grams (1 mole) of carefully dried and finely pulverized benzanilid (fused just before using). The contents of the flask are thoroly mixed by shaking, and if the materials were perfectly dry, no reaction takes place. The flask is then heated on an electric hot plate, first gently, then more vigorously, and fumes of HCl are evolved. After an hour with occasionally shaking, the evolution of HCl is much slower and the top of the condenser is provided with a calcium chloride tube. The mixture is then allowed

to reflux gently until no more fumes of HCl are evolved. The contents of the flask are then poured into a 250 cc. Claissen bulb, and the $POCl_3$ is removed by vacuum distillation. The product is then distilled off under as low a pressure as possible and solidifies in the receiver. The fraction below 185° at 32 mm. consists mainly of $POCl_3$ and is discarded. The fraction from 186° to 198° was collected for conversion to the imide cyanide, of which over 95 percent distilled at 196° under 32 mm. The yield was 97 grams or 85 percent of the theoretical.

4. Preparation of Benzanilid Imid Cyanide.[33])

90 grams of benzanilid imid chloride (1 mole) are dissolved in 300 cc. of dry petroleum ether and are mixed with a concentrated aqueous solution of 70 grams of NaCN (3 moles). The mixture is shaken for 24 hours in a shaking machine and the mixture is then filtered to remove any benzanilid formed by the hydrolysis of the imid chloride, and the layers are then separated. The ether layer is evaporated to dryness and the imid cyanide remains as brown crystalline plates. The yield of crude product is over 90 percent. The crude material is crystallized from boiling 95 percent alcohol, and the yield of pure material is 50-65 grams. Care must be taken not to use too large an excess of alcohol since the imid cyanide is fairly soluble in cold alcohol. The melting point of the product is 71°. That recorded in the literature is 72°. Impure material may be obtained from the mother liquor but was too impure for use. In this preparation either ethyl or petroleum ether (B.P. 30°-50°) may be used. The latter has the advantage of being obtained dry very easily, and of not dissolving appreciable amounts of water. Ethyl ether has the advantage of dissolving the imid chloride more readily but the disadvantages that the last trace of alcohol is removed with difficulty and this instantly hydrolyzes the imid chloride; also, water is appreciably soluble in ether and thus during the course of the reaction more hydrolysis takes place in this solvent than in the case of petroleum ether.

Both of these solvents were tried out and it was found that petroleum ether was more satisfactory since it yielded a purer product and gave slightly better yields.

Hydrolysis of Benzanilid Imid Cyanide.

(a) 5 grams of benzanilid imid cyanide (M.P. 71°) were refluxed gently for two hours with 20 cc. of 25 percent (by volume) sulfuric acid. A white crystalline solid was deposited in the mouth of the condenser, and white flaky crystals separated out on cooling the mother liquor. The acid mother liquor was extracted with ether and a white crystalline substance remained on removal of the ether. The crystals were removed from the mouth of the condenser and their M.P. was found to be 121°-121.2°. The crystals from the ether extraction without any further purification had a M. P. of 119-120°. Evidently both substances were benzoic acid M. P. 121.2°.

The mother liquors were made alkaline with NaOH and again extracted with ether. On evaporation of the ether a brown oil remained which was aniline; characterized by its acetyl derivative.

It is probable that if the hydrolysis were carried out by more mild hydrolyzing agents or for a shorter period of time, the intermediate products might be isolated to determine whether the anilide or nitrile group were hydrolyzed first.

(b) 5 grams of imid cyanide (M.P. 71°) were heated for two hours with 20 cc. of 25 percent NaOH and at the end of this time the dark oily layer of imid cyanide had apparently remained unchanged. The mixture was cooled and the unchanged imid cyanide filtered off. This material was dried between filter papers and had a M.P. of 67-69°, showing that apparently some decomposition had taken place. The recovered material amounted to over 90 percent of the original material showing that the imid cyanide is stable toward hot aqueous alkalies.

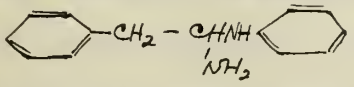
5. Reduction of Benzanilid Imid Cyanide.

50 grams of the imid cyanide are dissolved in 750 cc. of boiling absolute alcohol in a flask provided with a reflux condenser and an efficient mechanical stirrer. The contents of the flask are heated to vigorous boiling and the source of heat then removed. 120 grams of sodium are now added as rapidly as possible without too great a loss of alcohol thru the condenser. After all of the sodium has been added (about 45 minutes) and is completely dissolved, the mixture is cooled slightly and 750 cc. of water are cautiously poured in. The alcohol is then distilled off, from the steam bath and the residue is cooled and extracted with ether. The ethereal solution is then dried over sodium sulphate.

(a) Preparation of the free amine.

The dried ethereal solution is evaporated as far as possible from the steam bath, and the residual brown oil is distilled in vacuum. The greater part of the amine boils at 193°-194° at 30 mm. and amounts to 40 grams. About 5 grams of low boiling material were formed which was not further investigated. The free amine was crystallized from petroleum ether and forms clusters of needles, melting at 35°. The yield was 70 percent of the theoretical.

(b) Preparation of the amine hydrochloride

The dried ethereal solution from a second run is saturated with dry hydrogen chloride, the precipitated hydrochloride is filtered off, and washed with dry ether. The yield of the hydrochloride was 48 grams, or 77 percent of the theoretical. Since it is evident from the boiling point of the amine, 193°-194° at 35 mm. pressure, that it is not phenylethyl amine, whose boiling point is 198° at 754 mm., it seems probable that it is a diamine of the following structure: . This compound may form a mono or dibasic salt with acids, and it was therefore necessary to determine whether the hydrochloride obtained above was a mono or dihydrochloride. The material was analyzed

by the method of Stepanow and gave the following results:

Calculated	Percent Chlorine	Found
$C_{14}H_{16}N_2.HCl$	14.2	I . . . 14.02
$C_{14}H_{16}N_2.2HCl$	24.9	II . . . 13.85

These data showed without doubt that the salt formed was the mono hydrochloride.

(b) Attempted Acid Reduction of Benzanilid Imid Cyanide.

Mendius[34]) found that nitriles may be reduced by means of zinc and hydrochloric acid (or sulphuric) and by this means he reduced propionitrile, valeronitrile and benzonitrile, but the yields obtained by this method were much poorer than when the alkaline method was used. Since the alkaline reduction of the imid cyanide did not hydrolyse off the anilide group it was thought worth while to try an acid medium since under these conditions the anilide group might be readily hydrolysed off and not reduced.

50 grams of the imid cyanide were dissolved in 300 cc. of hot 95 percent alcohol, and added to the warm mixture of 125 grams of zinc, 500 cc. of 50 percent alcohol, and 300 grams of concentrated hydrochloric acid (1.19) which was stirred vigorously with an efficient mechanical stirrer. The reaction proceeded very slowly and after 30 minutes it could be seen that hydrolysis was taking place faster than reduction. For this reason it was deemed advisable to use a more vigorous agent and as a result 45 grams of magnesium, (sticks) were added as rapidly as possible. This caused a vigorous reaction.

On cooling the acid reaction mixture and extraction with ether it was found that a large amount of the material was of an acidic nature. This material was not further investigated. The solution was then made alkaline with 30 percent NaOH and again extracted with ether. On evaporation of the ether several drops of a dark brown oil remained which was probably aniline. This shows that the acid reduction with zinc or magnesium under the above conditions is not satisfactory and does not yield the desired product, due largely to the hydrolysis by

the acid.

6. Experiments with 1,3 Dichlorohydrin.

The dichlorohydrin used in these experiments was prepared by the action of sulphur chloride on glycerol, and altho it was distilled twice it still retained a slight odor of SO_2. The object of the following experiments was to try out the methods and determine the limitations of the reactions as well as the yields in the various steps.

(a) Method of Delepin.[35])

30 grams of dichlorohydrin are dissolved in 100 cc. of chloroform and 60 grams of dry hexamethylene tetramine are added. The mixture is refluxed gently for 48 hours and finally oily drops of a dark viscous substance separate out. The mixture is cooled, the solid filtered off and the filtrate discarded (after determining that 4 or 5 grams of solids remained in the filtrate).

The material obtained above was refluxed gently with successive portions of 1 volume concentrated hydrochloric acid, and 3 volumes of alcohol, until no more methylene diethyl ether is given off. It could be seen from the behavior of the solution on addition of the alcoholic HCl that the amine hydrochloride was not very soluble in this mixture, therefore the reaction mixture was treated with two volumes of alcohol and dry HCl passed into the solution for 5-10 minutes. The mixture heats up and on cooling, white clusters of needles separate out. These were filtered off, dried and kept in a desiccator over calcium chloride. This material was thought to be the hydrochloride of s-diamino isopropyl alcohol. The latter has been prepared by Gabriel and found to melt at 184.5°. The material obtained above remained solid at 220° and thus is not identical with the compound prepared by Gabriel, from s-dichlorohydrin and potassium phthalimid. Sufficient time did not remain for the identification of the material obtained above, but it is the intention of the writer to determine the nature of the substance later.

(b) Gabriel's Phthalimid Method.

It has been shown by Gabriel that the diphthalimid derivative of s-dichloroacetone is very slightly soluble and therefore difficulty hydrolyzed. He was able to prepare only a very small amount of s-diamino acetone by this method. It has been shown later by this author that in the reaction of dihalogen compounds with potassium phthalimid, that if excess of the halogen compound is used a monophthalimid monohalogen compound may be obtained; for example, with 1.5 dichloropantane. In the latter instance four moles of halogen compound are used with one mole of potassium phthalimid, and even then considerable amount of the diphthalimid derivative are formed.

30 grams of potassium phthalimid (1 mole) are treated with 90 grams of dichlorohydrin (4.5 moles) and heated at 180° for several hours. A white solid separates out and at the end of this time the mixture is cooled and poured into several hundred cc. of water. The excess of dichlorohydrin is removed by steam distillation and the mother liquor on cooling is filtered. The white of slightly colored substance obtained may be recrystallized from boiling water and in this manner a sample was purified and it was found to be the diphthalimid derivative, since its melting point was the same as that of the compound obtained by Gabriel using equimolecular amounts of the reacting substances. Evidently this method cannot be used for the preparation of a monophthalimid derivative. The yield of the diphthalimid derivative was about 35 grams.

7. Bromination of Diacetyl and its Monoxim.

Ten and three-fourths grams of Diacetyl are dissolved in 100 cc. of carbon disulphide, dried over $CaCl_2$, and a solution of 20 grams of bromine in 50 cc. of carbon disulphide are added, in small portions. Hydrobromic acid is evolved and the mixture heats up considerably. The carbon disulphide is evaporated off on the steam bath at 95° and the residue solidifies to a brown mass melting about 110°. This substance is evidently not monobromo diacetyl but the

dibromodiacetyl, melting at 116°; consequently another method must be used.

Farkas and Diels[37]) obtained the monobromo derivative of the monoxim of diacetyl by the direct bromination of diacetyl monoxim in methyl alcohol in solution. This method was tried and found to be satisfactory although the yields are not good.

25 grams of diacetyl monoxim are dissolved in 50 cc. of absolute methyl alcohol and cooled to about 0° in a large deep casserole. The theoretical amount of bromine is then added all in one portion; a very violent reaction takes place and considerable material will be lost at this point if a small casserole is used. The reaction mixture is then allowed to stand for a short while and is then poured into ice water. A dark brown oil is formed which solidifies and is removed by filtration. The yield is about 40 percent of the theoretical. From this compound through the acetate hydroxy diacetyl monoxim may be obtained in fair yields, and this may be converted to a thio glyoxaline by condensation with thiourea.

8. Condensation of Chloroacetophenone with Thiourea.

Since hydroxy ketones react with thiourea to produce thio glyoxalines, it was suggested that halogen ketones might react in the same manner. 8 grams of thiourea and 16 grams of chloroacetophenone are dissolved in 30 cc. of absolute alcohol and refluxed for 30-40 minutes. The mixture is then cooled and white needles separate out. These are filtered off and washed with ether. The yield was 18 grams.

It was found after this reaction had been carried out that this is a general reaction for the preparation of thiazoles, and the compound obtained was an amino thiazole, and not a thio glyoxaline; consequently it will be necessary to convert halogen compounds to the hydroxy compounds before condensing them with thiourea.

Conclusion.

The method of preparation of glyoxaline 4,5 dicarboxylic acid has been studied and improvements in the method have been suggested. The preparation of glyoxaline 4 carboxanilid has also been carried out.

The preparation of benzanilid imid chloride and imid cyanide have been studied and the conduct of the latter toward acids and alkalies was investigated. It was found to be unaffected by hot alkali, but was completely hydrolyzed by acids with the formation of benzoic acid and aniline.

Attempts were made to prepare the monophthalimid derivative of 1,3 dichlorohydrin, and it was found that the diphthalimid derivative was the only one formed whether a large or small excess of dichlorohydrin was used.

Monobromodiacetyl monoxim was prepared and attempts were made to brominate diacetyl directly, but these failed due to the formation of dibromo diacetyl although no excess of bromine was used.

The condensation of thiourea with an alpha halogen ketone was carried out and found to give excellent yields of the product, which is supposed to be an amino thiazole.

It was finally decided that the methods best suited for further study were: (1) the bromination of diacetyl or its oxim and formation of amino diacetyl, or direct condensation with formamidin (2) the preparation and reduction of glyoxaline carboxanilid imid cyanide (3) from methyl glyoxaline by partial oxidation and conversion to glyoxaline methyl alcohol or glyoxaline formaldehyde.

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